

Cholinergic Antagonists

نبتی حامیة الفزارة
بلا ۵۵۵

- = cholinolytics
- = parasympatholytics
- = cholinceptor antagonist

* دودة اوى
* التسميات دى

زى ال agonists ال antagonists برده

divided into muscarinic & nicotinic subgroups on the bases of their specific affinity to receptors.

Cholinolytics

Antinicotinic

Ganglionic blockers
(↓ clinical uses)

Neuromuscular junction blockers

Antimuscarinic agents (↑ clinical uses)

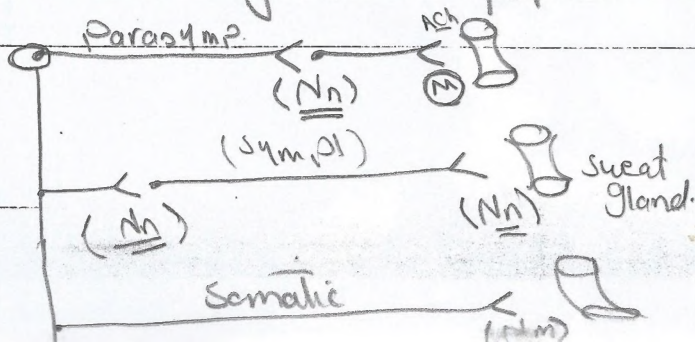
عادة لما يتقوى
cholinolytics
antimuscarinic agents.

* Nicotinic Receptor

(1) - ganglionic R < symph. Parasymp.

(2) - Nm. neuromuscular junction (somatic)

(3) - Sweat gland at synapse



Antimuscarinic Agents

① mainly Atropine (prototype)

(d.l. ⁺hyoscyamine) → Racemic mixture
found in Datura stramonium

② Scopolamine

(L-hyoscyne) levo

found in Hyosyamus niger

I Antimuscarinic agents

اسم:

- * The naturally occurring muscarinic receptor antagonists: atropine (prototype) → اسم: اس. فو. اس & Scopolamine

→ are alkaloids of the belladonna (Solanaceae) plants.
- Preparations of belladonna have been used for many centuries by physicians.

- Atropa belladonna

leaves ↓

= cuts the
thread of life

= women to dilate
their pupils

racemic mix.

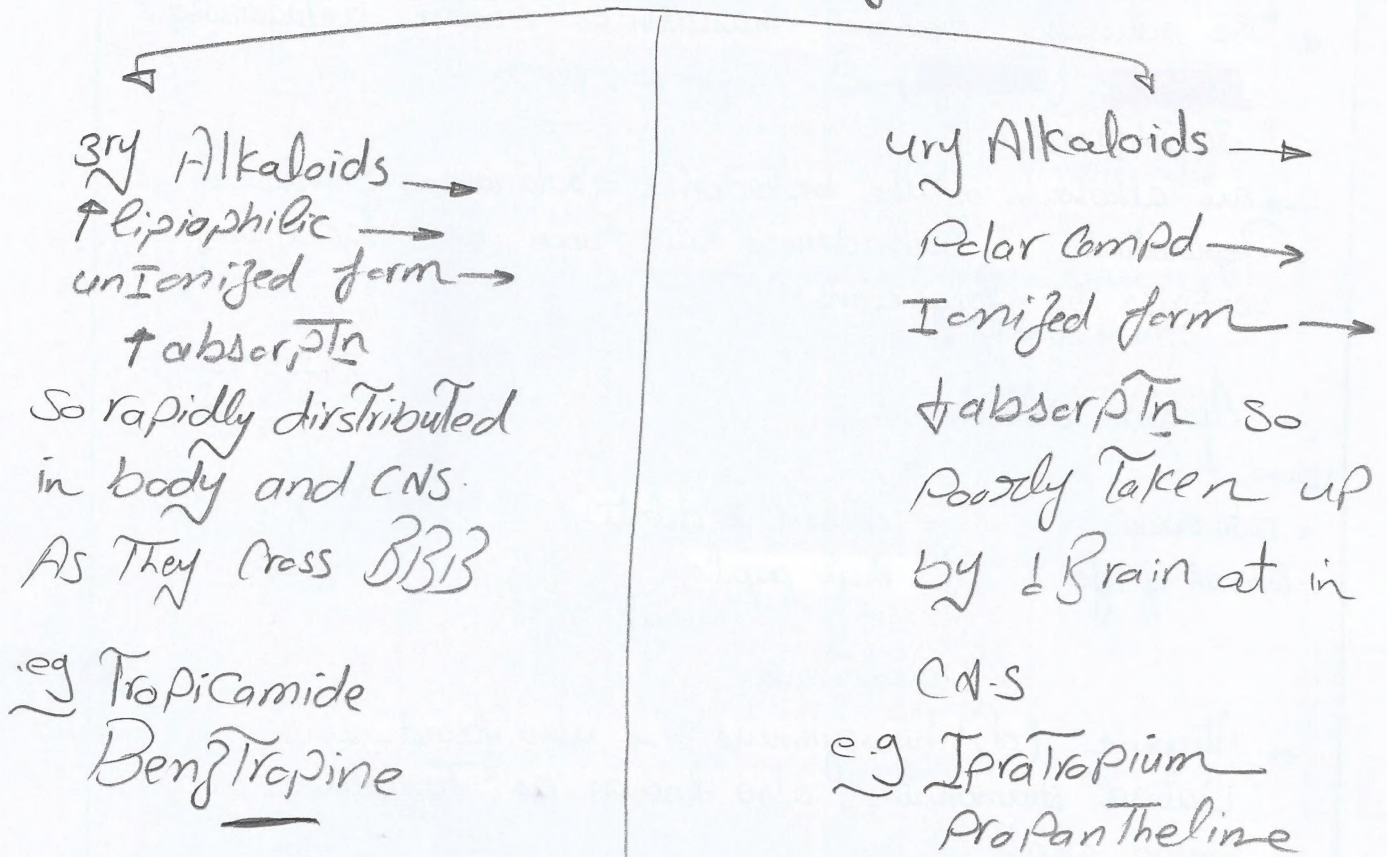
- * Atropine (d,l hyoscyamine) is also found in Datura stramonium, also known as Jamestown or Jimson weed.

levo ↓

- * Scopolamine (l. hyoscine) is found chiefly in Hyoscyamus niger (henbane)

- * A variety of semisynthetic & fully synthetic molecules have antimuscarinic effects.

* Pharmacokinetics of Anti muscarinic



Atropine

→ Disappear rapidly from blood
half life → 2 hrs

→ So drug effect & rapidly in organs

except in eye → 72 hrs why??

due to [Passive mydriasis]

unresponsive to light

Atropine → Radial muscle → Passive mydriasis

Trospicamide

(a) Kinetics :

التي هو تأثير الجسم على الدواء - اول ما نشوف
العنوان ده - تفكر في ال absorption, distribution له يعني ٥٥٥

* The natural alkaloids and most ^{3ry} antimuscarinic drugs (tropicamide, benztropine) are well absorbed from the gut and conjunctival membranes (eye) → widely distributed in the body & rapidly distributed into the CNS (as it can cross BBB) ^{↑ lipophilic (non ionized) ↑ absorption}

كل ده احنا عارفينه لان ال 3ry بيقت more lipophilic وهو ده
التي بيحصل ال absorption لكن

* In contrast, the ^{1ry} derivatives (1pratropium, propantheline) are poorly taken up by the brain & therefore are relatively free - at low doses - of central effects.
CNS - مش بيوصل

* Atropine disappears rapidly from the blood, with a half life of 2 hrs
من بيقتل كثير في الدم

• The drug's effect declines rapidly in all organs except the eye (72 hrs)

طب اشبعه بقى ؟
الاول - الادوية دي parasympatholytics بيقتل ايه في العين ؟

mydriasis (Dilatation) المرفوف

مخ ؟

هي فعلا بتقل كده بين بتقل نوع اسمه Passive mydriasis
mydriasis بين unresponsive to light - يعني لما بتعرض لظن

المرء من سبب ال mydriasis
فيعتبره ديسر لم اعرف

Non
Selective
Blocker
 M_1, M_2, M_3, M_4, M_5

* MOA of Atropine

→ Competitive blocker of muscarinic R

↓
overcome by ↑ Dose of muscarinic Agonist

→ Tissues highly sensitive for Atropine
Salivary - bronchial - sweat

But Parietal cells (Stomach) ↓ sensitivity

ال pupil من حتميت ، فالإنسان به من يتقدر بفتح عينه في الشمس وهو به الذي يجعل للناس الذي يروح تكشف قاع العين .
 يقع ٢ أيام تقريباً من عارف يسوف كويس . وده لان ال atropine يفضل كسر في العين .

• من النوع الثاني الذي هو ال active mydriasis .
 من هيق responsive to light . انراي ١٥ mydriasis .
 by constriction of constrictor pupil muscles .
 أمال ايه العضلات التي بتعمل املاً ال mydriasis .
 Radial muscles are resp. for mydriasis

⑥ MOA:

* Atropine and related compounds cause competitive blockade of muscarinic receptors .

• blockade by small doses of atropine can be overcome by a larger conc. of muscarinic agonist .

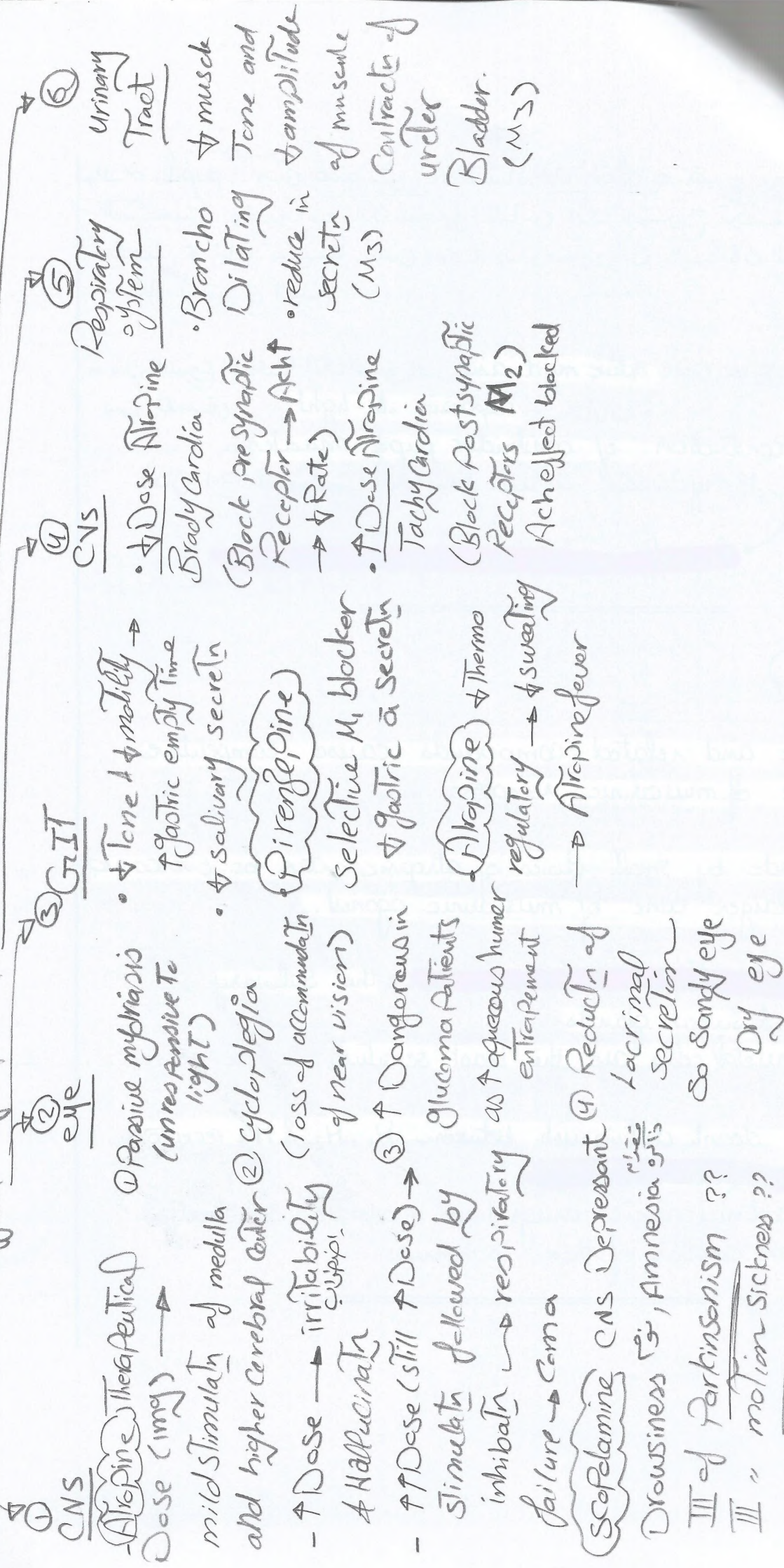
* Tissues most sensitive to atropine are : the salivary , bronchial & sweat glands .

Gastric parietal cells are the least sensitive .

* Atropine doesn't distinguish between M_1 , M_2 & M_3 receptors (i.e. Non selective blockade)

Other antimuscarinic drugs have moderate selectivity for one or another of these subgroups .

effect of Atropine :-



1. CNS

2. Eye

3- GIT

4 - CVS

5. Respiratory system.

6. Urinary Tract

1. CNS :

* Atropine in therapeutic doses (1mg) causes only mild excitation as a result of stimulation of the medulla and higher cerebral centres.

Toxic doses lead to restlessness, irritability & hallucinations. With still larger doses → stimulation is followed by depression → leading to circulatory collapse, respiratory failure & coma.

* Scoopolamine → causes CNS depression manifested as drowsiness (احساس بالنوم) and amnesia (نسيان الاشياء)

E drolisiness
E amnesia

(التهال الريحان)

- Scopolamine is used for Parkinsonism as it results from excess cholinergic activity because of deficiency of dopaminergic activity in the basal ganglia striatum system.

!!S. os. Qul.

* However, in the presence of severe pain → the same doses of scopolamine can occasionally cause excitement, restlessness & hallucinations.

* Motion sickness → involve muscarinic cholinergic transmission

motion sickness ← فاضح ال receptors ال ← بيت اقفل ال

∴ Scopolamine is often effective in preventing or reversing these disturbances.

2. EYE :

احنا كنا انكنا عنها شوية مع ال atropine لما قلنا اننا
بتعمل passive mydriasis ← نقول الكلام ده تاني
وتزود عليه حبة حاجات ههه

1) Passive mydriasis (dilation of the pupil) → unresponsiveness
to light (photophobia) → يعني بيخاف من الضوء لأنه
مش بيقدر يفتح عينه من الضوء

2) Cycloplegia (= loss of accommodation for near vision)
↓
ده الذي بتعمله ال parasympathetic وانا بقفلها ← فهو قفاري

3) In patients with glaucoma → IOP (Intraocular pressure)
may rise dangerously.

طبيب ليه ؟
احنا كنا قلنا المصاهرة الرابعة ان ال parasympathetic بتعمل myosis
يعني contraction في ال circular وال ciliary m. وقلنا ان ده
بيفتح ال canal علشان ال aqueous humor يخرج ← علو كده ؟

انا لما اقفل ال receptors دي بقت ← كل اللي فوره ده مش هيحصل
يبقى مش هيخرج خلل من ال aqueous humor يبقى ال IOP هتزيد

طبيب لو هو عنده glaucoma يعني ايه ؟
من ال aq. humor ← يبقى لما اقفل ال receptors كمان ←
الدنيا هتتوقف خالص ← يبقى ال IOP هتزيد اوى

حاولوا تفسروا كل حاجة كده ، ما تحفظوش وخلص ههه

4) Reduction of lacrimal secretion leads to dry or "Sandy" eyes.

بَعْدَ الْحَجِّ كَأَنَّ فِيهِ رَمَلَةً وَغَيْرَهَا .

3. GIT ::

* ↓ tone & motility → ∴ gastric emptying time is prolonged & intestinal transit time is lengthened.

مغروفہں تکون عارفین لیہ ؟

هتفكر بنفس الطريقة ٥٥٥ دي parasymp.rec ← يبقى هتقل
ايه ولا GIT ؟ ← يبقى اما اقفله ← هتجمل ايه ؟!

- * Salivary secretion is significantly reduced, however, gastric secretion is blocked less effectively.

* Pirenzepine (Selective M_1 blocker) & a more potent analog \rightarrow \downarrow gastric acid secretion with fewer adverse effects of atropine.

- * Atropine suppresses thermoregulatory sweating & muscarinic receptors at the end of sympathetic cholinergic fibres innervating sweat glands → "atropine fever".

تعالوا تفهم النقطة الأخيرة دي القرآن سورة ٥٥

فاكرين احنا كنا قلنا قبل كده ان ال sweat gland فيها استثناء

cholinergic (muscarinic) vs sympathetic (α) receptors

↓ sweating يعني ↓ blood flow to skin sympathetic effect

وال effect parasympathetic effect العكس ← يعني ↓ sweating (thermoregulatory) وده مهم جداً علشان يثبت درجة حرارة الجسم

فلما اقل ال receptors دي ← فاستج ال sweating وبالتالي درجة حرارة الجسم هتعالى اوى وده اسمه Atropine fever

4. CVS : (Cardiac Vascular system)

- low doses → initial bradycardia as it inhibits presynaptic receptors on vagal fibres

هو لما يقل ال presynaptic receptors اللى بيقل خروج ال Ach ← يعني ال Ach هيزيد ← اللى هنا على القلب بيقل ال rate ← فتقل bradycardia طبع لو زودت الجرعة!

- larger doses of atropine → cause progressively ↑ tachycardia by blocking vagal effects on M_2 receptors (postsynaptic) on the SA nodal pacemaker

يعني لما الجرعة بيزيد ← بيشتغل على ال M_2 recop ← دي postsynaptic يعني لما يقلعها ← هيقفل تأثير ال Ach ← اللى المفروض يقل ال rate ← يعني ال rate هيزيد ← يعني هيجل tachycardia

انا عارفة اني بطول اوى عليكم ← بسى معلش علشان لازم تكونوا فاهمين كويس اوى ← استحملوني معلش

5. Respiratory System :

- Both smooth muscles & secretory glands of the airway receive vagal innervation & contain muscarinic receptors.
- Atropine causes \rightarrow bronchodilation & reduction of secretion (M₃ receptor)

وده لان ال parasymp سفل bronchoconstricts وبتزود ال secretions
يقل وده سفل الغلى على طول ..

6. Urinary tract :

- M₃ receptor mediate detrusor muscle contraction.

∴ Muscarinic antagonists \rightarrow ↓ the normal tone & amplitude of contractions of the ureter & bladder.

طرح احنا كده خلايا ال Pharmacological effects
نستوف ال Therapeutic uses
فان ليا

* Therapeutic uses :-

1] Bronchial asthma (COPD) chronic obstructive Pulmonary Disease.
- Bronchodilator So used in cold mixture

as anti Histaminic

- Ipratropium → inhalation as have ↓ adverse effect Than Atropine in mucociliary clearance as it is dry.

2] overactive urinary Bladder disease

III nocturnal enuresis ^{السَّوَالِ}
urinary incontinence ^{السَّوَالِ}

- Flavoxate - oxybutynin → as Transdermal

- Imipramine → TCA Tricyclic Antidepressant & antimuscarinic effect

→

3] GI →

• Anti Spasmodic (ureter - uterus - biliary tract)

→ Hyoscine - N-butyl bromide - propantheline

clidinium - oxyphenonium - Isopropamide

• anti diarrhea and in irritable bowel

→ Flavoxate - oxybutynine

• III of Peptic ulcer

→ Pirenzepine (selective M₁ Blocker)

4] Eye → To produce mydriasis and cycloplegia

But Homatropine - Cyclopentolate and Tropicamide are preferred Than Atropine & Scopolamine as have low duration of Actn

5] CNS

→ III of Parkinsonism Antipsychotic (D₂ blockers)
eg Benztropine - Biperide - Tri Hexyphenidyl (3ry amines)

→ III of Motion sickness Scopolamine → B/B/B

→ Anesthesia → ↓ Salivary - bronchial secretion
Atropine

6] Cholinergic Poisoning

Effect of organophosphates - Atropine 1-2mg I-V every 5-15 mins
signs appear (Dry mouth, miosis)

(d) Therapeutic Uses:

يمكن استخدامه للتق:

1. Bronchial asthma
2. Urinary tract diseases
3. GIT
4. Eye
5. CNS
6. cholinergic poisoning.

تعالوا نكلم عن واحدة التفر:

1. Bronchial asthma, COPD: (Chronic Obstructive Pulmonary disease)

- * Ipratropium (administered by inhalation) → donot produce adverse effects on mucociliary clearance as does atropine.

وه لا يـ 4ry فـ من الـ absorption
atropine الـ adverse effects الـ
atropine الـ
more potent but non selective

- * Antihistaminics in "cold" mixtures are due primarily to their antimuscarinic properties.

بيستخدمون في ادوية البرد علاه بـ توسع الشعب الهوائية
تخف

2. Overactive Urinary^{bladder} disease : , nocturnal enuresis^{تبول ليلي} , urinary incontinence^{التبول اللاإرادي}

has parasymp effect . انا عايز اقلل ال urination ينقص اقلل ال
يستخدم parasympatholytics ال

* Flavoxate , Oxybutynin → as transdermal , shows

lower incidence of side effects (dry mouth & eyes that limit tolerability & continued use)

* Imipramine (TCA = tricyclic antidepressants with Antimuscarinic action)

antimuscarinic action . هذا هو الدواء للاكتئاب . بين ال dry effect ال
"nocturnal enuresis" ال

3. GIT :

1) Antispasmodic (biliary tract, ureter & uterus) →
use Hyoscine, N-butylbromide, Propantheline,
Clidinium, Oxyphenonium, Isopropamide (try amines,
that are less absorbed & has no central effect)

2) Irritable bowel , Antidiarrhoeal , Excessive salivation :

use Dicyclomine , Flavoxate , Oxybutynin .

3) Peptic Ulcer → Pirenzepine → has relative selectivity for M_1 receptors and limited penetration into the CNS.

4. Eye:

To produce Mydriasis & cycloplegia (loss of accommodation for near vision) → Homatropine, Cyclopentolate & Tropicamide are preferred to topical atropine or Scopolamine, due to their shorter duration of action.

علامة زى ما قلنا ان ال atropine بيقتد لفترة طويلة (72 hrs) فياخد المريض ويفضل يحاشى منه مدة ، لكن الادوية دي قصيرة فأحسن

5. CNS:

1) For Parkinsonism, extrapyramidal side effects of antipsychotics (D blockers)

ال antipsychotics بيقتل ال D receptors وال Dopaminergic receptors

اللى فى عكس ال cholinergic receptors . طب اننا هنا لازم استنسخ ال 3ry cpds علشان اننا عازمة التأتير فى ال CNS

use : Benztropine, Biperiden & Trihexyphenidyl → 3ry amines that gain access to the CNS

2) For motion sickness → Scopolamine (pass bbb) prophylactically & transdermal

3) For Anesthesia → Atropine (premedication to block responses to vagal reflexes induced by surgery or neostigmine & to reduce salivary and bronchial secretions during the surgery)

لا يقلل إفرازات الغدد اللعابية و اللعاب في مجرى الدم
 لا يقلل إفرازات الغدد اللعابية و اللعاب في مجرى الدم
 لا يقلل إفرازات الغدد اللعابية و اللعاب في مجرى الدم

6. Cholinergic poisoning:

as CNS, peripheral effects of organophosphates (cholinomimetics)

→ ttt: Atropine sulfate → given as: (dose)

- 1-2 mg IV every 5-15 mins until signs of effect appear (dry mouth, reversal of miosis)
- as much as 1g/day may be required for as long as 1 month for full control of muscarinic excess.

c Therapeutic uses

دواء مضاد للتشنج و لحد من إفرازات الغدد اللعابية

g- Interactions

e- Adverse effects

f- contraindications

ADverse Effect

- ① Sandy eye
- ② Blurred vision
- ③ Dry mouth
- ④ Tachy Cardia
- ⑤ Constipation
- ⑥ Hot and flushed skin

→
CNS

- ① Drowsiness
- ② Confusion
- ③ Hallucination
- ④ Delirium → Followed by depression
respiratory failure → Coma.

⑨ Adverse effects :

اغلبها حاجات قلنا في النصف واحد ما شيين

1. dry mouth
2. blurred vision زغلة
3. "Sandy eyes"
4. hot and flushed skin
5. tachycardia
6. Constipation
- central effects as:
7. Restlessness
8. Confusion
9. hallucinations
10. delirium (معيش فكري)

↓
may progress to depression, collapse of the circulatory & respiratory systems → death

وعلاوة على ذلك الحفظ ← فيه جملة كنه توصف الانا الى
عنه adverse effects دي :

(1) dry as a bone , blind as a bat , red as a beet ,
mad as a hatter (7→10) (2,3) خفاش (4) بجر
رجل معنوه او معنونه

* Contra indicata *

- 1- Glucema
- 2- Prostatic enlargement
- 3- Jeuer
- 4- Tachy Cardia

* interACTn *

① Antimuscarinic + Drugs have anti-muscarinic.

Anti Histaminic $\searrow \uparrow$ Anti muscarinic effect
Anti Depressant \rightarrow Tri cyclic
Anti psychotic \rightarrow pheno Thiazine

② Antimuscarinic + MAOIs

$\searrow \uparrow$ Anti-muscarinic effect

③ Antimuscarinic + Parasympathomimetic

\searrow
Counteract each other

④ Antimuscarinic (\searrow gastric sec.) affect
 \downarrow absorp_n of other Drugs.

⑧ Contraindications - Precautions :

- 1- Glaucoma
 - 2- Prostatic enlargement (urinary retention)
 - 3- Paralytic ileus
 - 4- Fever
 - 5- Tachycardia
- لأننا قلنا انه هيزود ال IOP أوى
 علنا اهل ال prostatic enlargement ال
 صعبة فما يفتح اديه كمان ال
 كمان بقلوا ال urination
 لأنه هو يسبب الجلطات دى
 فلو المريض عنده اهل دى ، لو
 اخذ الادوية دى هيزيدوا أوى
 خطر .

وآخر عنوان فى ال antimuscarinic agents :

⑨ Interactions :

- 1- The effects of atropine & other antimuscarinics may be enhanced by the concomitant use of other drugs with antimuscarinic properties, such as :
 some antihistamines , phenothiazine antipsychotics & tricyclic antidepressants .
- 2- MAOIs (Monoamine oxidase inhibitors) may enhance the effects of antimuscarinics
- 3- The reduction in gastric motility caused by antimuscarinics may affect the absorption of other drugs .
- 4- Antimuscarinics & parasympathomimetics may counteract each other effects →

طلب احنا كده خالص اول نوع من ال antagonists اللى هو ال
antimuscarinic وعرفنا عن كل حاجة تقريباً وعرفنا ان ده اهم gp
تخالوا نشوف تاى gp وهو:

II Antinicotinic drugs

و اول نوعين

Ganglionic blockers

ده بيشتغل على ال

ganglia

بين ال junction اللى

بين ال nerves عموماً

دعوة بالمنطقة اللى بين

ال nerve وال muscle

وبالتالى هو nonselective

ممن هيقدر بين بين

sympathetic or parasymp.

ganglia

هياثر على ال استرني وبالتالى

ممن بيستخدم كثير

Neuromuscular blockers

ده بيشتغل على ال neuromuscular junction.

اللى بين ال nerve ending

وال receptor اللى على ال muscle

وبالتالى دول more selective عن

التانيين وبيستخدموا أكثر شوية

كده فكرة عامة عن الاسترني ، يلا تشوف واحد واحد كده بالتفصيل
شوية ٥٥٥ ٥٥٥ ٥٥٥

Antinicotinic Drugs

Ganglionic Blocker

• Nn

• Non Selective \leftarrow Symp. Para-Symp.

• Ion Channel Coupled R.

e.g. (1) Nicotine

Dil

Conc.

- Stimulatory effect

is complexed \leftarrow Sy. Par.

- \uparrow B.P. - \uparrow secret. - \downarrow B.P.

- \uparrow Heart Rate - \downarrow Heart Rate

as it stimulate

- \downarrow GI+ Activity. Bladder

\downarrow Ganglionic To produce

Epinephren-N-E

(2) Trimethaphane

• Short duration

• I.V infusion

• Competitive Nicotinic

Ganglionic Blocker

(3) Meclizamine

• long duration

• orally (Adv)

• Competitive

Blocker

Neuromuscular Junction Blocker

Nm \rightarrow skeletal m.

Drugs

Central muscle Relaxant

\downarrow

e.g.

• Diazepam \rightarrow binds \bar{e} GABA

• Dantrolene \rightarrow Directly Acting on muscle interfer \bar{e} Ca^{++} release

• baclofen \rightarrow Act on GABA

Ach analogue

Competitive Nm Blocker

Antagonist

Non De-polarizing

\downarrow bind \bar{e} R and Block

\downarrow Act relax

non Comp.

Nm Blocker

Agonist

De-polarizing

\downarrow bind \bar{e} R and give \bar{e} same Act. of Ach at 1st

\downarrow Contraction but not Broken down So \downarrow relax

e.g. Succinylcholine

Ganglionic Blockers

* Ganglionic blockers specially act on the nicotinic receptors, probably by blocking the ion channels of the autonomic ganglia (N_N receptors) → المصاحبة

* These drugs show no selectivity towards the parasympathetic or sympathetic ganglia & not effective as neuromuscular antagonists

∴ the responses observed are complex and unpredictable, making it impossible to achieve selective actions
تفسي الكلاز الال قلا الصفة الال فالت

∴ Ganglionic blockers are rarely used therapeutically today. However, they often serve as tools in experimental pharmacology.

* طبيب تناولوا شوف ٢ امثلة لادوية بيستغلوا ال mechanism
ومشي كتكلم فيهم كتر ٥٥٥

A * Nicotine *

* A component of cigarette smoke, Nicotine has many undesirable actions.

* Depending on the dose, nicotine depolarizes ganglia, resulting 1st in stimulation followed by paralysis of all ganglia.

i.e. at low dose (dil nicotine) \rightarrow stimulation

stimulatory effects are complex

كائنات - خالدة على السعير
sympathetic + parasymp.

includes: \uparrow in blood pressure & cardiac rate

طبع و نسخہ !؟

علاوة على ذلك، يستقبل ganglia الـ
noradrenaline, epinephrine، adrenal gland الـ
التي تستقبلها على الـ sympathetic في القلب، ويؤدي
↑ B.P & ↑ cardiac rate.

2 - ↑ peristalsis & secretions

parasymp. effect.

لما يزود الـ

⑧ at higher doses (conc nicotine) → paralysis of all ganglia

causes : 1 fall in blood pressure due to ganglionic blockade.

2 Activity both in the GIT & bladder musculature ceases

impulses ganglionic receptors
symp or parasymp neuromuscular junction
effect

(B) * Trimethaphan *

* It is short acting, competitive nicotinic ganglionic blocker that must be given by IV infusion

↓
agonist dose أكبر من الـ agonist
أكثر

* Today, the drug is used for the emergency lowering of blood pressure when other agents cannot be used.

(C) * Mecamylamine *

زكا الدفون

* produces a competitive nicotinic block of the ganglia

* long duration of action (10 hrs)

* The uptake of the drug via oral absorption is good in contrast to trimethaphan.

active orally & long duration of action : ألي ألي ألي

ganglionic blockers كلها الـ

الـ نسوف تاف نوع
↓

2 Neuromuscular Blocking drugs

* These are drugs that block the cholinergic transmission between motor nerve endings & the nicotinic receptors on the neuromuscular end plate of skeletal muscle.

نفس الكلام الى قلناه في التقسيمه الى علنا من شوية

* النوع ده من ال blockers عبارة عن structural analogues of Ach يعني علنا يعرف بمسك في ال receptors بتلصق ال Ach لازم يكون شكله شوية ، طب بعد ما بمسك ؟ ممكن يشغل بطريقة من اتية ؟

① يا إما antagonist او non-depolarizing وده الى احنا عارفينه العاصي يعني ، الى همسك في ال receptors ويمنع انه يحول depolarization ويكده يبقى قفله وده تأثيره هيباير على طول على هيئة relaxation مثلا في ال muscles. ⑤ النوع الثاني بقى بيتي agonist او depolarizing طب اترى هيفل blocking ؟ هو همسك الاول في ال receptor وهدية تأثير زي ال Ach يعني مثلا contraction ، طب وبعدين ؟ ال acetyl cholinesterase العاصي انه بعد ما يعمل كده ، يتفك ويتكسر ال cholinesterase لكن هنا مش هيعمل كده ، الدواء ده هيفضل لازم في ال receptor ومشي هيسيب فنج شوية ال receptor هيتعب ويبطل بيجت impulses وبالتالي هيعمل زي paralysis وال muscle هيفل relaxation زي ايه احنا ؟ ال succinyl choline او ال suxamethonium فومتوا كده ؟

لو فهمتوا الكلام كلمة الى فوه ، يبقى الجزء الجاي ده هيبقى حلو
أوى ان شاء الله . . .

* These neuromuscular blockers are structural analogs of acetyl choline & act either as - antagonists (non depolarizing type) or agonists (depolarizing agonist) at the receptors on the endplate of the neuromuscular junction.

* Neuromuscular blockers are clinically useful during surgery to produce complete muscle relaxation without having to use higher anaesthetic doses to achieve comparable muscular relaxation.

st. analog of Ach is muscle relaxants

* A second gp of muscle relaxants, the central muscle relaxants → used to control spastic muscle tone.

These drugs include:

1) diazepam (binds to GABA receptors)

الكتور مشرحواش بين احنا احناها في العلى ، الى عايز يفهمها يرجع لللى او يجي نشرحواله علينا ما نطولش هنا

2) Dantrolene → acts directly on muscles by interfering with release of Ca from the Sarcoplasmic reticulum.

3) baclofen \rightarrow probably act on GABA receptors in the CNS.

نشوف الهمه يبد ← كنهكم عن %

4. Non depolarizing (competitive) blockers

2. Depolarizing (Non-competitive)

* Non Depolarizing Nm Blocker

* Competitive Nm Blocker

[1] e.g. Curare and Tubocurarine Alkaloids

[2] MoA → AT ↓ low dose → Block Nm R → ↓ muscle contractn
This Actn overcome by ↑ ACh (by cholinesterase inhibitor (physostigmine, Edrophonium))
→ AT ↑ dose → Block Nm R and also block Ion channel on end plate so ↓ Ability of cholinesterase inhibitor Drugs to reverse effect of Competitive Blocker ↓

[3] Actions

rapidly appear on small muscles of face and eye
→ fingers → neck, limb, Trunk → intercostal muscle (blast) → Diaphragm (paralysis)

[4] Therapeutical uses

is anesthesia to ↓ Dose of it during surgery

[5] Pharmacokinetics . neuromuscular Blocker Taken only I.V??

as Absorption orally is minimized

• Poorly penetrate cell membrane & BBB

• most Drugs excreted unchanged (no metabolism)

e.g. Tubocurarine - Pancuronium - mivacurium - doxacurium

• Atracurium Degraded spontaneously in plasma by ester hydrolysis

• Vecuronium • Rocuronium → Deacetylated in liver

So Their clearance are prolonged if Patient is hepatic disease

[6] Adverse Effect . Tubocurarine → ↑ Histamine release
(broncho spasm - hypotension - ↑ salivary secretin)

• promotes ganglionic Blocker → ↓ BP

[7] Drug interaction . cholinesterase inhibitory ↓ Dose → ↓ Blocking
↑ Dose → ↑ "

Block Na⁺ channel ← • Halogenated hydrocarbon anesthetics
Compete with Ca⁺⁺ Ion → ↑ ACh • Aminoglycoside Antibiotic (gentamycin, Tobramycin) ↑ -
↓ ACh ← • Ca Channel Blocker

(A) Non depolarizing (competitive) Blockers :

* هو نفس الكل إلى قلبه قبل كده لكن شيت اتولكم انه بيتقى competitive يعني لو زوت ال Ach هيسيله ويتعد مكانه لكن ال depolarizing ده non competitive يعني مش هيتأثر بال Ach لأنه هو أصلاً طريقه شغله انه يسبك لفترة لمبرلة في ال receptor مكانه يشله ، لكن لو كان competitive بيتقى لو زوت ال Ach ، ابق بوظفته ومش هيدى التأثير اللى هستنيه منه

* تعالوا نكتب الكلمتين دول ٥٥٥ بين الاول نشوف حته كده دراسات اجتماعية عن اكتشاف الادوية دي ٥٥٥

* The 1st drug that was found capable of blocking the skeletal neuromuscular function was "Curare"

which was used by the native hunters of the Amazon in South America to paralyze animals.

كانوا بيعطوه في السهام اللى بيصطادوا بيها الحيوانات

② "Tubocurarine" was ultimately purified and introduced into clinical practice.

* The neuromuscular blockers have significantly ↑ the safety of anaesthesia, since less anaesthesia is required to produce muscle relaxation.

يعني الاول كانوا بيدوا جروعة كبيرة من التخدير علشان يعمل muscle relaxation قبل العمليات ، لكن له مخاطره .
لكن بعد ما اكتشفوا ال neuromuscular blockers اللى بتعمل relaxation بروه ، بقوا بيستخدموها مع ال anaesthesia وبالتالي تقللوا الجرعة محتاجينها للتخدير.

a. MOA:

1. at low doses:

- * Nondepolarizing neuromuscular blockers combine with the nicotinic receptor & prevent the binding of ACh → ∴ prevent depolarization of the muscle cell membrane & ↓ muscular contraction.

وهذا الكلام الى قلبنا قبل انه ، ان يبيح ويبيح مكان ال ACh على ال receptor وبالتالي يمنع depolarization ← يمنع contraction

- * Because these agents compete with ACh at the receptor → they are called "Competitive blockers".

This action can be overcome by increasing the conc of ACh in the synaptic gap, for example by administration of cholinesterase inhibitors (∴ ↑ ACh) such as: neostigmine, or edrophonium.

دائرة التخدير
→ Anaesthesiologists often employ this strategy to shorten the duration of the neuromuscular blockade.

نحن احنا قلنا اننا بيستخدمك muscle relaxant
الجراسية على انه اقل ال dose يباع ال anesthetic ، طب العروق خلعت ،
عائزة افك ال blockers بدل بقى على انه يقصر يعمل contraction تاف
← ادوية cholinesterase inhibitor ← يزيد ال ACh ← يسهل ال blockers
ويعمل مكانها ← يعمل contraction

طب ده ال low dose ← كل ال كحيز ال كحيز ال
receptor ← طب لو زودت ال dose ، كحيز ال كحيز ال ؟

2. At High doses :

* Non depolarizing blockers block the ion channels of the end plate → this leads to further weakening of neuromuscular transmission & reduces the ability of acetylcholinesterase inhibitors to reverse the action of non depolarizing muscle relaxants

يعني اي 15

يعني لو زودت ال dose بتاعت ال NM blockers دول
 عن ايت قتل ال receptor وفتح ال ACh عيكت فيها ، لا ده
 كمان هيقفل ال ion channels اللى موجوده على ال endplate بتاعت
 ال muscle ← طب ممكن حد يسأل زود ال ion channels اللى فابتها
 املا مادام ال blockers دي قافله ال receptors ؟
 عن طريق ال cholinesterase inhibitors
 . هيقول ايت ده competitive ، يعني لو زودت ال ACh هيسيل
 ال blockers من ال receptors وبعيكت مكانها ، بين مفروض نجد انه
 ايت بين ال effect بتاعه عن طريق ال ion channels علشان يحصل depolarization
 وبعدين يحصل contraction ← يعني هنا صدادى ال channels دي مقفولة
 no contraction ← no depolarization ←

b. Actions :

اسرع عمليه هتستغل عليها وبين عليها التأثير

① Small, rapidly contracting muscles of the face and eye are most susceptible & are paralyzed 1st

↓
followed by

② the fingers

↓
③ limbs, neck & trunk muscles.

↓
④ the intercostal muscles are affected

↓
and lastly,
⑤ the diaphragm muscles are paralyzed

c. Therapeutic uses:

- * These blockers are used as adjuvant drugs in anesthesia during surgery to relax skeletal muscle.
• وعرفنا انهم على انه اقل ال dose ياتى المجر الى عن
• toxicity لو زاد ، اتقاس به باني الى معاه ال blockers الى
• relaxation. - معاه

d. Pharmacokinetics:

عن ايه اجبار ال absorption وال metabolism وال excretion ياتى
الانوية الى .

- * All neuromuscular blocking agents are injected intravenously, why?
because their uptake via oral absorption is minimal.

* They penetrate membranes very poorly and do not enter cells or cross the bbb

* Many of these drugs are not metabolized → their actions are terminated by redistribution.

For example,

tubocurarine, pancuronium, mivacurium & doxacurium are excreted in the urine unchanged.

* Atracurium is degraded spontaneously in the plasma & by ester hydrolysis.

* The aminosteroid drugs as: Vecuronium & rocuronium → are deacetylated in the liver → and their clearance may be prolonged in patients with hepatic diseases.

These drugs are also excreted unchanged in the bile (i.e. through feces)

e - Adverse effects:

* d-tubocurarine may induce histamine release (eg: bronchospasm, hypotension, excessive bronchial and salivary secretion) as a direct action on the mast cell rather than IgE mediated anaphylaxis.

* The drug can also promote ganglionic blockade & lower blood pressure

neuromuscular junction ایہ جگہ ایہ nicotine receptors ایہ جگہ ایہ

لكن لما ال dose بزيادة ← ال selectivity بتقل فممكن
تتقل مكان ال nicotinic receptors اللى بي ال ganglia

← ال sympathetic إلى القلب ← لها اقفل ال ganglionic receptor

blood pressure ← ضغط الدم

E Drug Interactions :

طبیعی آن ای حاجه مساعد ای زاده ال Ach ← تقر هتاکس
التأثیر بتلهم وای حاجه تقل ال Ach او تساعد ای فصل ال ion channels

يَبْقَى هَسْلَبُهُمْ وَتَزُودُ ثَأْنُهُمْ.

1) Cholinesterase inhibitors: drugs such as neostigmine, physostigmine and edrophonium $\rightarrow \uparrow \text{ACh}$

oo can overcome the action of non depolarizing neuromuscular blockers but with elevated dosage but, cholinesterase inhibitors can cause a depolarizing block as a result of elevated ACh conc. at the end plate membrane.

یعنی ما افقولی ای ایلده chol. inhibitors کسکی علاجه تسکیل کویسی
ال blockers من علی ال receptors ← لان که ال ACh (فیزی اوی) ←
صحیح تسکیل ال blocker دکن ال ACh که هو الی هیدر blocking

2) Halogenated hydrocarbon anesthetics: drugs such as halothane act to enhance neuromuscular blockade by exerting a stabilizing action at the neuromuscular junction.

ارای؟

ان anesthetic دڼ بېقفلوا او Na channels وپاتلای بڼوډو
NM blocking تائیر او

3) Aminoglycoside antibiotics: drugs like gentamicin or tobramycin \rightarrow \downarrow acetylcholine release from cholinergic nerves by competing with Ca^{+2} ions. so they synergize with tubocurarine and other competitive blockers, enhancing the blockade.

احیاناً عارضی او ان Ca^{+2} پیچ او او vesicles او مزج او Ach وځلایا دتلاک او antibiotics او دې بڼل Competition او Ca^{+2} وپاتلای بېقل تلوع او Ach \leftarrow Ach \leftarrow بڼ بڼوډو تائیر او blockers.

4) Ca channel blockers: these agents may \uparrow the neuromuscular block of tubocurarine & other competitive blockers as well as depolarizing blockers.

په:

1) cholinesterase inhibitors: low dose \rightarrow \downarrow blocking
high dose \rightarrow \uparrow blocking but by Ach.

2) Halogenated hydrocarbon anesthetics?
3) aminoglycoside antibiotics
4) Ca channel blockers

\uparrow blockade effect

⊕ الفرق بينه وبين الالفات ① الالفات antagonism يعني عكس شغل
 الـ Ach لكن به اصلاً agonism يعني اول ما دميك بيدي نفسي
 التأسيس يتبع الـ Ach

(۴) الی قات کان
nondepolarizing
depolarization دے گا، ی ای Ach
depolarization پہلے contraction دے گا، ی ای Ach
acetylcholinesterase دے گا، ی ای Ach
paralysis دے گا، ی ای muscle

a. Mechanism of action: } منقول في حاجة جديدة

* The depolarizing neuromuscular blocking drug, succinylcholine \rightarrow attaches to the nicotinic receptor and acts like Ach to depolarize the junction but, unlike Ach which is instantly destroyed by acetylcholinesterase, the depolarizing agent persists at high conc. in the synaptic cleft \rightarrow remaining attached.

* Depolarizing Nm Blocker *

* Non Competitive Nm Blocker *

[1] e.g Succinyl Choline. Suxamethonium

[2] MOA - Binds to NmR and give same Act_n of Ach at 1st but not hydrolysed by Cholinesterase so due to continuous contraction \rightarrow Paralysis
- once binding \rightarrow Depolarization (Na-channel opening)

Phase I

\downarrow
Transient Twitching of muscle
 \downarrow
gradually

To Paralysis

Phase II

\downarrow
Spastic Paralysis
(due to \uparrow contraction)

[3] Actn • respiratory muscle are paralyzed last like Competitive
• Succinyl Choline have short duration of Actn why??
As rapidly broken by plasma Cholinesterase
• Does not lead to ganglionic Blocker even at \uparrow Dose
• have weak Histamine release

[4] Therapeutic use • used when endotracheal intubation is required
 \rightarrow as it have rapid onset and short duration of Actn
to avoid aspiration of gastric content during intubation

[5] pharmacokinetics • Succinyl Choline \rightarrow I.V infusion
rapidly hydrolysed by plasma Cholinesterase

[6] Adverse effect • Apnea \rightarrow due to deficiency in plasma esterase \rightarrow diaphragm paralysis
• Hyperthermia

to the receptor for relatively long time & providing a constant stimulation of the receptor.

* The depolarizing agent 1st causes the opening of the Na channel associated with the nicotinic receptors, which results in the depolarization of the receptor.

→ Phase (I) → this leads to transient twitching of the muscle (fasciculations)

(contraction) (انقباض)

↓ Ach. اللى سببها الجزء اللى سببها phase I

The continued binding of the depolarizing agent renders the receptor incapable of transmitting further impulses going way to gradual paralysis

→ Phase (II)

Spastic paralysis (انقباض مستمر) contraction (انقباض) spasm (انقباض)

b. Actions:

* The sequence of paralysis may be slightly different, but as seen with the competitive blockers, the respiratory muscles are paralyzed last.

* Succinyl choline initially produce short lasting muscle fasciculations, followed with few mins by paralysis

* The drug does not produce a ganglionic block, except in high doses, although it does have weak histamine releasing action.

* Normally, the duration of action of succinyl choline is extremely short, since this drug is rapidly broken down by plasma cholinesterase.

احنا قلنا انه من بيتكسر بال acetylcholinesterase في الدم و acetylch. في العضلات
بيتكسر بال cholinesterase في الدم و plasma.

C. Therapeutic uses:

* Because of its rapid onset & short duration of action
→ succinyl choline is useful when rapid endotracheal intubation is required during the induction of anesthesia.

بعض ساعات مع التحنيط، باختيار ادخل tube في trachea
على ان التنفس - فاكون محتاج حاجة تقدر ان paralysis بسرعة
بس لمدة قصيرة - ده الى بيحل ال succinyl choline
طرح ليه فتجاه يكونه لمدة قصيرة !

to avoid aspiration of gastric contents during intubation
بعض انا بسيل العفلات فتمكن ال gastric contents تخرج من ال sphincters
فكانه كده غاي حاجة سرعة .

* It is also employed during electroconvulsive shock treatment
من عارفة يعني ايه

d. Pharmacokinetics

Succinyl choline is injected intravenously, its brief duration of action (several mins) results from rapid hydrolysis by plasma cholinesterase.

It is usually given by continuous infusion.

e. Adverse effects

1. Apnea

توقف التنفس

A genetically related deficiency of plasma cholinesterase or presence of an atypical form of the enzyme can lead to apnea due to paralysis of diaphragm.

2. Hyperthermia

ارتفاع درجة الحرارة

When halothane is used as an anesthetic, administration of succinyl choline has occasionally caused malignant hyperthermia (with muscular rigidity and hyperpyrexia) in genetically susceptible people.

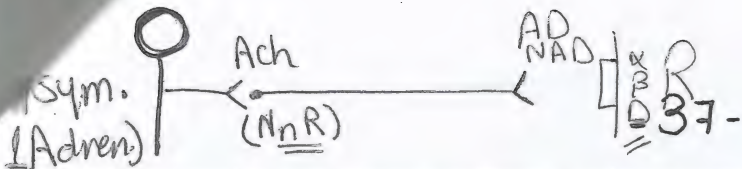
Parasympathetic system → ألف مبروك → احنا خلصنا الـ
Agonists, antagonist → بكل ما فيه

Sympathetic system → افضل شوية بنا → علشان هتبدى فى الـ

تصيح → افضل الـ Parasymp. كله عن الـ Symp.

وذاكر مواضع → من محاضرات → علشان متلخبطين

يعنى افضل انك تفصل الجزء القادم عن المحاضرة وتعتبر محاضرة جديدة



Pharma (6) ✓

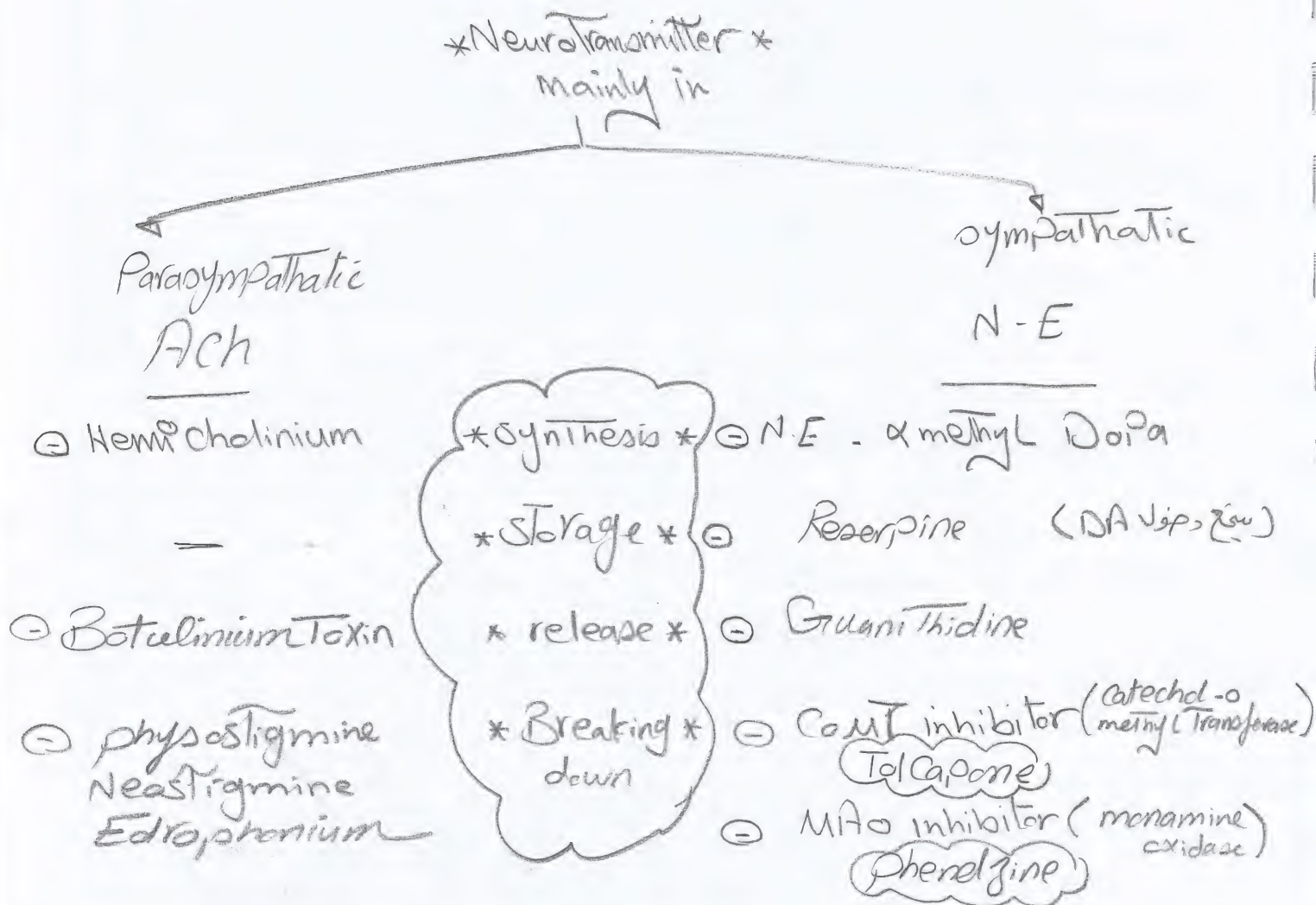
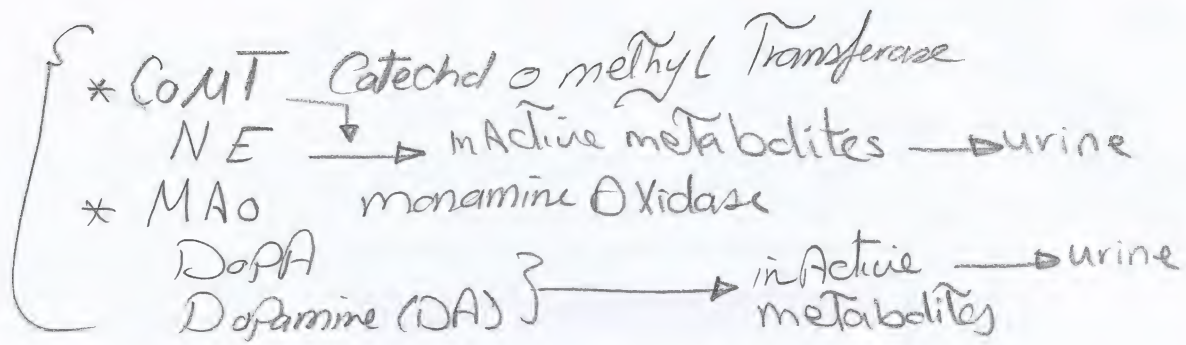
Sympathetic System

آعلا نفكر مع بعض حبة حاجات كده من غير ما نبقاش بنسكف
زي ال

- * It's very imp. part of A.N.S. that controls actions during stress situations as Fright, Flight, Fight (3F)
- * it's innervatn, comes out From thoraco lumbar region of spinal cord → (T₁ - L₄) → with short preganglionic nerve fibre, long postgang. one.
- * Ganglionic receptor is cholinergic (Nicotinic neuronal)
- * effector organ " " adrenergic (α or β or D → dopaminergic) where its neurotransmitter is Norepinephrine mainly
- * Adrenal medulla was considered as a modified ganglion → receiving neurotransmitter from preganglionic nerve fibre & → producing Adrenaline neurotransmitter in the blood.

إحنا أخذنا في المحاضرة الرابعة مراحل تكوين وخروج
Acetyl choline من ال cholinergic nerve fibres

من آعلاوا تسوف بنا مراحل تكوين وخروج ال Norepinephrine
من ال Adrenergic nerve fibre



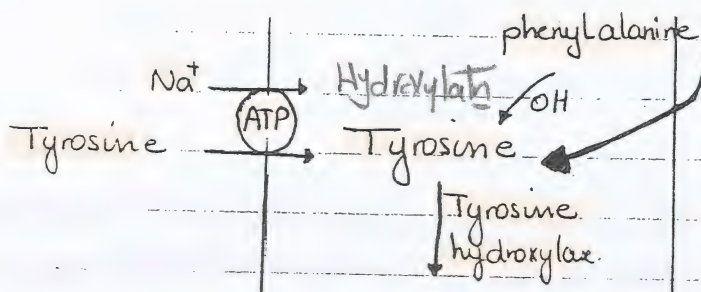
p.37

- 4 -

بموا ٥٥٥ الرسمة دي الى كانت موجودة في : . المحاضرة السادسة
بل كانت ظلمة في التصوير ٥٥٥ هنرسمها اتاني على شكل صورة
أوى ٥٥٥ اوعى تلمنقوها ٥٥٥ حلوها بقى في مكانها في المحاضرة ٥٥٥٥

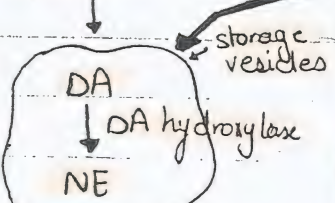
Noradrenergic Neurotransmission.

1 Synthesis of NE :



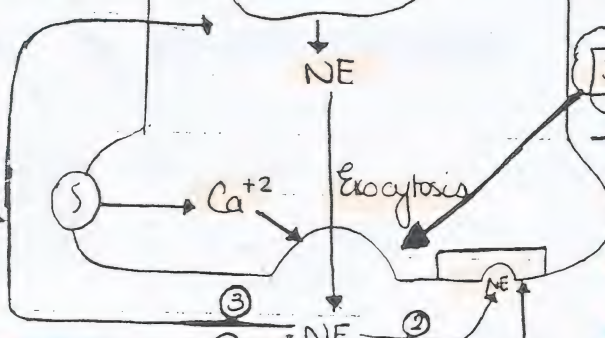
- Inhibited by NE
- لأن ال vessels مفيش مكان
- It is Rate limiting step.

2 Storage of NE :



- DA converted to NE
- Inhibited by Reserpine
- يقفل ال pump ال بتدخل ال DA جوة ال storage vesicles

3 Release of NE :



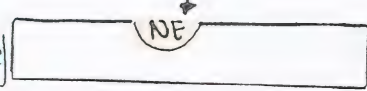
- activated by indirect sympathomimetic
- Inhibited by Guanethidine
- occur by effect of Ca^{+2} voltage dependant channels.

5 Reuptake into neuron :

- It is inhibited by Cocaine & TCA as imipramine

4 Binding to receptors :

- presynaptic α_2 receptor (autoregulation) \rightarrow release of NE
- Postsynaptic receptors \rightarrow effect.



N.B

- 1 main neurotransmitter in Adrenergic nerve fiber is **N.E** as it stored in vesical for short time so not sufficient time for methylation of N.E \rightarrow E.P. (Adrenaline)
- 1 main neurotransmitter in Adrenal medulla is **Adrenaline** as it stored in vesical for sufficient time to methylation occurs $NE \rightarrow E.P$ [Adrenaline]

* الرسالة التي فاتت دي من الى جانبها الكثير بالضبط بالحرف
* هو بس زور عليها حاجة واحدة

→ in adrenergic nerve fibre → NE → is stored in vesicles for a short time (not sufficient time) for methylation for adrenaline synthesis.

يعني ال NE مني بيلحق بـ methylate، علشان يتحول لـ adrenaline.

→ in adrenal medulla → NE → stays for along time → So it can be methylated by NE methyl transferase enzyme, adrenaline is formed

• the main product of adrenergic nerve fibres is NE. while that of adrenal medulla is adrenaline (epinephrine)

• لمبغاً لو مني فاهم أي حاجة في الرسالة → إحنا تمت أم حضرتك يا بامنا

• بمن يا سيدي • الكلام اللي جاي لم يقال في المحاضرة • إحنا جنبناه من ال Lippincott • بس بأمانة هيقدم معاك لو عرفتك • هتبقى فاهم • ويسهل عليك الحفظ جداً • إن شاء الله

Adrenoceptors

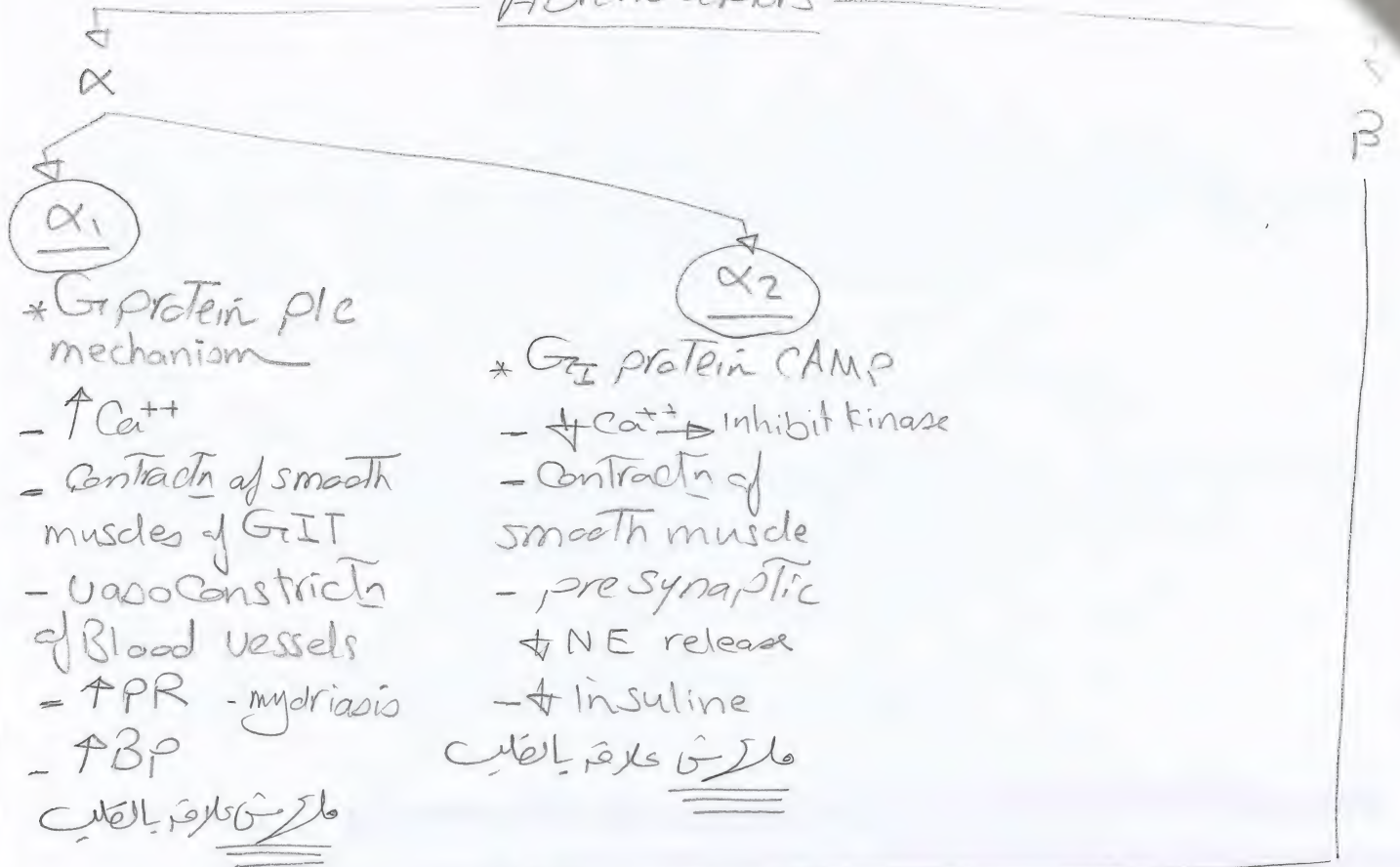
* In symp. system → there are several classes of adrenoceptors

* The main 2 types are α , β → were initially identified on the Basis of their response to adrenergic agonists → NE, E, isoproterenol.

ie, α respond to epinephrine > norepinephrine > isoproterenol.

, β " " isoproterenol > epinephrine > norepinephrine;

Adrenoceptors



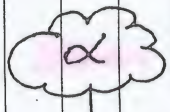
Adrenoceptors



* respond to epinephrine > norE > isoproterenol



* respond to isoproterenol > epinephrine > NE



* works by G protein PLC mechanism

↑ Ca^{+2} causing smooth muscle contraction

ملوس آى علاقه بالقلب
← له علاقه بالعضلات
smooth muscles

* Vasoconstrictn
* increase peripheral resist.
* increase blood pressure.
* mydriasis → radial Ms.



* works by G protein Adenylyl cyclase mechanism.

↓ Ca^{+2} in secretory glands.
↑ Contractn of smooth muscles

* inhibitr of NE release by mediating presynaptic inhibitr
ie α_2 receptor is the presynaptic receptor

* ↓ Secretn as ↓ insulin Secretion.



* Both β_1, β_2 work by G_s Protein Adenylyl cyclase mechanism

↑ Ca^{+2} in Cardiac muscle (β_1) → ↑ contractn
↓ contractn in smooth muscle (β_2) → Blood vessels

* Tachycardia
* increased lipolysis
* increased myocardial contractility.
* increased renin release.



* Vasodilatr
* slight ↓ in peripheral resistance
* relaxed uterine muscles (smooth)
* increased muscle, liver glycogenolysis.
* increased release of glucagon.

* u have to know that $\rightarrow \uparrow \text{Ca}^{+2} \rightarrow \text{muscle} \rightarrow \text{contract}$,
 $\rightarrow \text{Secretory gland} \rightarrow \text{Secretion}$.

* What's peripheral resistance? (PR)

Answer \rightarrow it's the resistance of the small arterioles to the flow of blood inside it.

- this occurs when those arterioles are constricted.

- PR is the main reason for \uparrow blood pressure (hypertension).

$\therefore \beta_2$ causes vasodilation $\rightarrow \downarrow \text{PR} \rightarrow \downarrow \text{Blood pressure}$.

α_1 causes vasoconstriction $\rightarrow \uparrow \text{PR} \rightarrow \uparrow \text{Blood pressure}$.

الحاجات دي لازم تفهمها كويس جداً في سياق ال M.O.A بتاع
أدوية الضغط كلها متلاق في الحاجات دي

* Distribution of receptors :

\rightarrow Some organs contains 2 types of receptors But only 1 predominates :

example : blood vessels of skeletal muscles contains :

① α_1 \rightarrow if sympathetic impulse received \rightarrow vasoconstriction,

② β_2 \rightarrow if " " " " \rightarrow vasodilation,

إيه رأيك فيم اللي هي سود على الثاني ؟

إنت لما تبجي تخافهم في عضلاتك محتاجة دم كثير ولا قليل ؟

أكبر دم كثير \rightarrow يبقى أكبر يحصل vasodilation \rightarrow يبقى أكبر β_2
هو اللي هي سود على الأول.

\rightarrow Some organs contain only 1 type of receptors as the heart
contains only β_1 \rightarrow sympathetically $\rightarrow \uparrow$ contract.

(Adrenergic Agonist) (Adrenergic neurotransmitter)

Sympathomimetics

Catecholamines

Derivatives of β -phenylethylamine
c1ccc(cc1)CCN

* Dopamine Oc1ccc(O)cc1CCN

* N-E Oc1ccc(O)cc1CCN(C)C

* E Oc1ccc(O)cc1CCN(C)C

* Isoprotrenol Oc1ccc(O)cc1CCN(C)C

→ rapidly deactivated by COMT
 → Post synaptic
 → gut wall

MAO → intra neuronally
 → gut wall, liver

→ Parenterally ineffective orally

→ Highly polar so not penetrate BBB

→ CH₃ gp in E & Isoprotrenol make them more potent for β Receptor

Non Catecholamines

* phenyl ephrin Oc1ccc(cc1)CCN(C)C

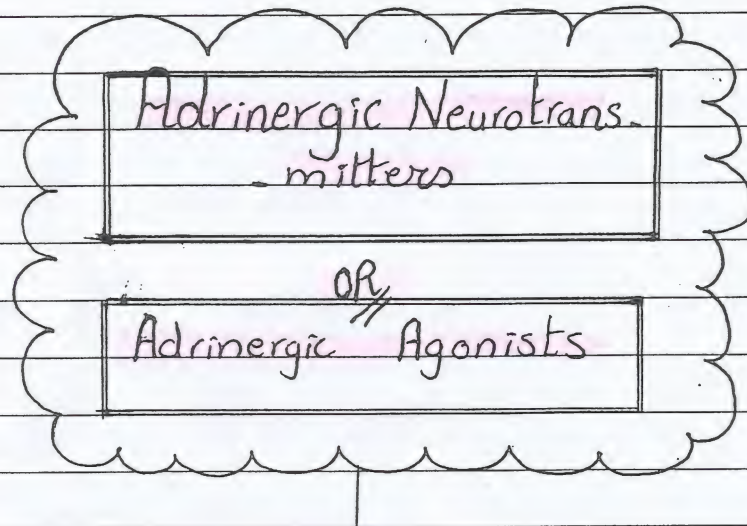
* Ephedrine Oc1ccc(cc1)CCN(C)C

→ ↑ duration of Actn as less susceptible for hydrolysis by MAO
 • Lipid soluble → BBB

* methoxamine COc1ccc(cc1)CCN(C)C

* Amphetamine Cc1ccc(cc1)CCN(C)C

د وقتي احيا خالصه ال Receptors دى و هيا على
Neurotransmitt. II



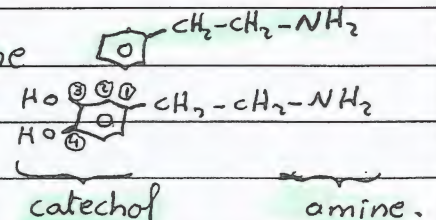
↓
a) Catecholamines

↓
b) Noncatecholamines

a) Catecholamines

* They are derivatives of β phenylethylamine

* They are 3,4 dihydroxybenzene derivatives



* Catecholamines include :

① epinephrine

② norepinephrine

③ dopamine

④ isoproterenol

* They are characterized by :

① high potency

② rapid inactivation by :

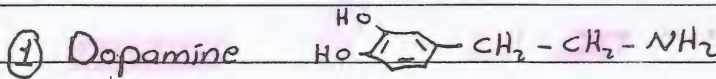
⊖ COMT postsynaptically , ⊖ MAO intraneuronally

⊖ COMT in gut wall , ⊖ MAO in liver, gut wall

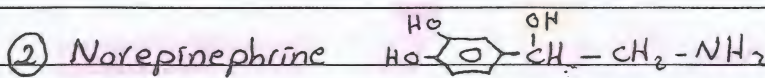
⊖ has brief period of actn, when taken parentally, ineffective orally

- * Catechol amines has poor penetratn, in the CNS as they are polar, don't penetrate BBB.

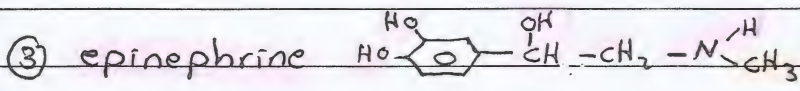
والوقتى نرسم ال structures بتاعهم + خليك ماشى ماليا هتلاقينى كل خطوة بتزود 1 group فباعد مركب جديد.



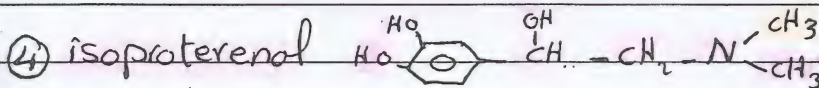
naturally occurring



زودت OH على ال CH₂



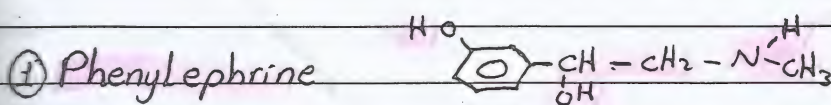
زودت CH₃ على ال (N)



زودت كمان CH₃ على ال (N)

* بصى بتا + ال (CH₃) الى فى ال epinephrine وال iso proterenol بتخليهم more potent على ال B + أكثر من ال Norepinephrine وال dopamine

⑥ Non catecholamines



فيه ال epinephrine بس فيه (OH)

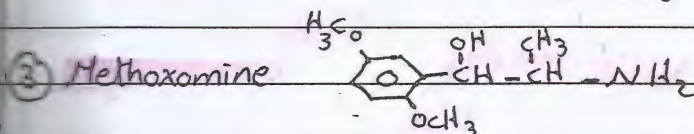
والصافه فقط على ال benzene



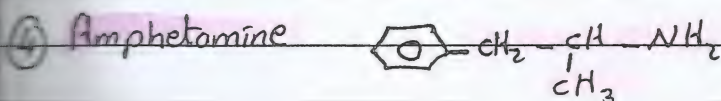
less susceptible to hydrolysis

by MAO so longer actn, than

catecholamines



More lipid sol. gives them access to CNS



Mechanism of Action

① Direct acting agonists:

حاجات بتدخل في المستقبلات receptor
وتعمل ال effect directly

- Bind directly to adrenoceptors, produces effect
- they include all catechol amines, phenylephrine from non catechol amines.

② Indirect acting agonists:

بتدخل جوه ال neuron ويعمل
stimulate ال release NE ال
اللي بيطلع والمستقبل في ال receptor ويعمل ال effect

- those enter the presynaptic neuron, causes the release of norepinephrine in synaptic cleft → Binds to receptor → gives the effect
- those include amphetamine, tyramine

③ Mixed acting agonists:

يعمل مستقيم ويعمل كانه مستقيم
كانه

- Can bind directly to adrenoceptors → giving effect
- Can cause the release of NE → & binds → effect
- those include ephedrine, metaraminol.

والموثر ال Direct acting والمستقيم ال
واحد فيهم مستوي كانه

Pray alot 4 US ooo

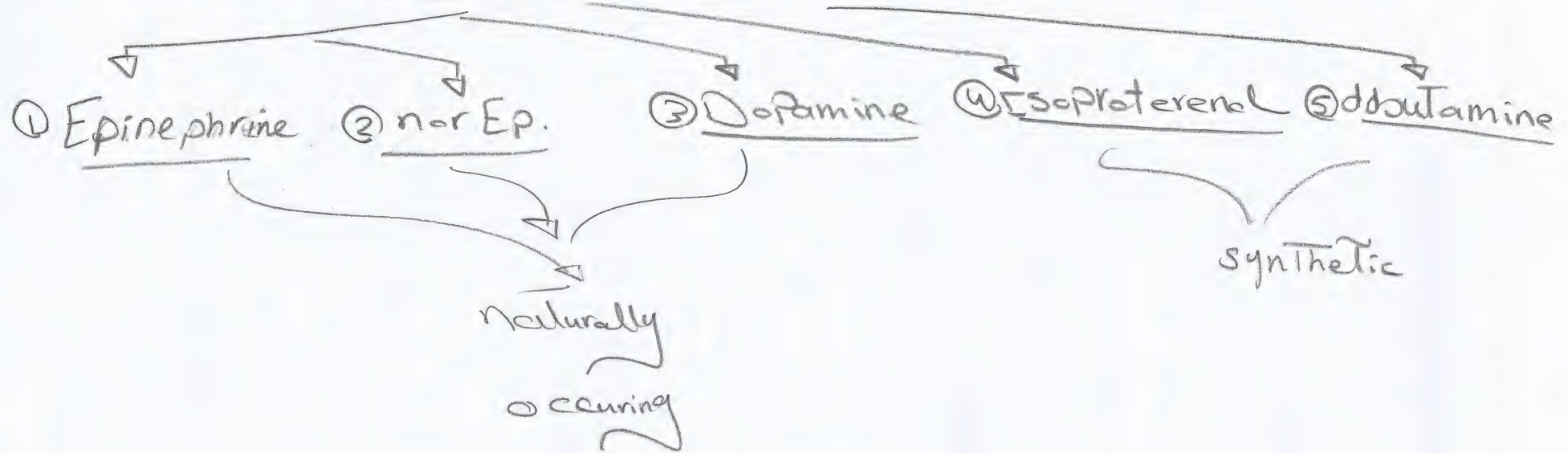
(mechanism of Adrenergic Agonist)

(A) Direct Acting Agonist

- Directly binds \bar{E} R \rightarrow effect

- include Catecholamines - Phenyl Ephrin of non catecholamines

تقلا انشوف ادك \rightarrow * catecholamines.



Direct acting Agonists

① Epinephrine

→ a) actions

→ b) Therapeutic uses

→ c) pharmacokinetics

→ d) Adverse effect

→ e) interactions.

* It's one of the 5 catecholamines :

epinephrine norepineph. dopamine dobutamine isoproterenol

naturally occurring

synthetic.

* It interacts with Both β , α receptors

→ at low doses → β effects predominates → Vasodilation,

→ at high doses → α effects " → Vasoconstriction.

a) Actions

i) CVS

ii) respiratory

iii) hyperglycemia

iv) Lipolysis.

i) Cardiovascular :

→ it ↑ contractility of heart (+ve inotropic) by β_1 effect → فكر
لسانك كنه كذا لازم نشرح ال receptors في أول الجزء ده لسانك تبقى فاهم
ومستعجب في الحفظ لسانك الحوار ده متلاقه في كل حده

→ it ↑ rate of heart (+ve chronotropic) by β_1 effect

∴ Cardiac output ↑

ده ال effect كل ال heart

A Actn

- ① CVS
 - β_1 effect \rightarrow +ve Inotropic (Contractility) \rightarrow +ve Chronotropic (Rate) \rightarrow \uparrow Cardiac output
 - β_2 effect \rightarrow Vasodilation of BVs \rightarrow liver & skeletal muscles \rightarrow \downarrow PR
 - α_1 effect \rightarrow Vasoconstriction of BVs \rightarrow skin & viscera & mucous membrane \rightarrow \uparrow PR \rightarrow \uparrow BP
 - \downarrow Renal Blood flow \rightarrow \uparrow Retention of H₂O & electrolytes \rightarrow BV \uparrow \rightarrow Cardiac output \uparrow
 - \uparrow SBP • \downarrow DBP
- ② Respiratory S
 - β_2 effect \rightarrow smooth muscles of Bronchial Vasodilation so III of asthma.
- ③ Hyperglycemia
 - \uparrow glycogenolysis in liver by β_2 effect
 - \uparrow glucagon release by β_2 effect
 - \downarrow insulin release by α_2
- ④ Lipolysis
 - lipolysis of adipose tissue by β_1 effect

① Epinephrine

• \uparrow Dose $\rightarrow \beta \rightarrow$ Vasodilation
 • \uparrow $\rightarrow \alpha \rightarrow$ " Constrictn

B Therapeutic uses

- ① Bronchial asthma
 - acute \rightarrow Epinephrine
 - chronic \rightarrow Selective β_2 Agonist (Terbutaline) as no effect on Heart
- ② Glucemia
 - as \downarrow production of aqueous humor by vasoconstriction of ciliary body BVs by α_1
- ③ \bar{e} anesthetics
 - To \uparrow duration of Actn of local anesthetics as it makes vasoconstrict at the site of injectn so allow local anesthetics to persist at site before absorption in systemic ci.

C Pharmacokinetics

- rapid onset of Actn
- brief duration
- deactivated by MAO & COMT
- I.V & S.C. endotracheal Tube - Inhalation - Topically in eye
- ineffective orally as deactivated by intestinal enzymes.

D Adverse effect

- ① CNS Disturbance
 - Headach. Tension
 - fear - Tremors
- ② Pulmonary edema
- ③ Cardiac arrhythmia (digitalis)
- ④ Cerebral Hemorrhage
 - \uparrow BP \rightarrow \uparrow PR \downarrow

E InterActn

- ① Epinephrine + Hyperthyroidism drugs
 - \uparrow CVS effect
- ② Epinephrine + Cocaine
 - \uparrow CVS effect
 - as Cocaine prevent uptake of neuron for E. so it bind ER for long time

* Selective β_2 Agonist *

Terbutaline

→ it constricts peripheral arterioles of skin, mucous membrane, viscera by α_1 effect → causes \uparrow PR → \uparrow BP

→ it dilates Blood vessels of Liver, skeletal muscles by β_2 effect → slight \downarrow PR

→ Renal Blood Flow is decreased

∴ retention of H_2O , electrolytes → increasing blood volume
→ increasing the cardiac output.

∴ The net effect of that on heart, Blood vessels is ∴

- ① \uparrow in systolic blood pressure → which depends on both cardiac output, peripheral resistance.
- ② slight \downarrow in diastolic blood pressure → which depends only on peripheral resistance.

ii) Respiratory ∴

→ it Causes powerful Bronchodilatation by acting on Bronchial smooth muscle by β_2 effect

→ it can be Life saving in individuals suffering from acute asthmatic attack as it relieves dyspnea rapidly

iii) Hyperglycemia ∴

→ Breaking ↓ glycogen in → glucose

→ it causes glycogenolysis in Liver by β_2 effect

→ " " \uparrow release of glucagon by β_2 effect.

→ " " \downarrow release of insulin by α_2 effect.

iv) Lipolysis :

→ it causes Lipolysis from adipose tissue by β_1, β_3 effects

لو مزاك الحكة بتاعت ال receptors في (39) page كويس من كتب خالص في حفظهم هنا و متلاقهم سهل جداً

(b) Therapeutic uses

- i) Bronchospasm
- ii) Glaucoma
- iii) Local anaesthetics.

i) Bronchospasm :

→ epinephrine is the primary drug in emergency treatment of acute asthma, anaphylactic shock.

→ However → Selective β_2 agonist as terbutaline are favoured (preferred) in treatment of chronic asthma as it has no effect on heart, has longer duration of action,

علامة ال heart على β_1 فـ

أنا غير أعالج العلام في أدوية خاصة selective علامة مقبولة ال heart معاً هو ماوش نوب

ال epinephrine من selective مقبولة استخدام في العلام ال chronic كـ مـ استخدام في العلام ال acute لأن حالة صعبة ومحتاج دواء قوى وهو ال epinephrine

ii) Glucoma :

→ epinephrine is used to reduce intraocular pressure (IOP) in open angle glaucoma as it reduces production of aqueous humour by vasoconstricting of ciliary body blood vessels by α_1 effect

يُضيقُ منقبي الجسم القزوي وجميع الأوعية الدموية في الجسم القزوي
كلها إلى الأوعية الدموية في الجسم القزوي

→ لذلك ينخفض blood flow في الجسم القزوي
في الجسم القزوي وجميع الأوعية الدموية في الجسم القزوي

iii) Anaesthetics :

→ anaesthetics soln, contain 1:100,000 parts of epinephrine
يحتوي محلول التخدير على 1:100,000 أجزاء من epinephrine
→ لذلك فإن vasoconstriction في الجسم القزوي
في الجسم القزوي وجميع الأوعية الدموية في الجسم القزوي
في الجسم القزوي وجميع الأوعية الدموية في الجسم القزوي

تقلل من سرعة دوران الدم في الجسم القزوي

→ The effect of epinephrine is to ↑ the duration of local anaesthetics
→ this is done by vasoconstriction at site of injection so allowing the local anaesthetics to persist at the site before being absorbed into circulation & metabolized.

→ also used to vasoconstrict mucous membranes to control oozing of capillary blood
يستخدم أيضا لـ تضيق الأغشية المخاطية للسيطرة على النزيف من الأوعية الدموية الصغيرة

© Pharmacokinetics

→ epinephrine has rapid onset of actn,
But Brief duratn, of actn,

- it's given intravenously For most rapid actn,
- also can be given → Subcutaneously or, endotracheal tube or, by inhalatn, or, topically in eye.
- oral administratn, is ineffective since all catecholamines are inactivated by intestinal enzymes.

④ Adverse effects

- i) CNS
- ii) haemorrhage
- iii) cardiac arrhythmias
- iv) pulmonary oedema.

i) CNS disturbances :

* anxiety * fear * tension * headache * tremors.

ii) Haemorrhage :

→ it may induce cerebral haemorrhage as ① their vessels are very thin, ② due to ↑ BP ③

iii) Cardiac arrhythmias : → especially if patient is receiving digitalis

iv) Pulmonary edema

© Interactions

- i) hyperthyroidism
- ii) Cocaine

i) Hyperthyroidism :

- epinephrine → may have enhanced CVS actn, in patients with hyperthyroidism.
- ∴ if it's required in such patient → the dose must be reduced.

ii) Cocaine :

- epinephrine → may produce ↑ CVS actn, in presence of Cocaine
- because Cocaine prevent the uptake of catecholamine into the neuron
- So, it remains at the receptor site for longer period.

gallia epinephrine ll lipia lianl aul
- jano juo g jaw aul do all n! jassl

Levorterenol (2) Norepinephrine

adrons

Therapeutic uses.

- it affects α receptors more than β receptors

(CH₃) Guloriss n lile

- Norepinephrine is called also Levorterenol

② nor Epinephrine [levorterenol]
- more potent for α Receptor as it not contain CH₃ gp

A Actn

- α_1 effect \rightarrow Vasoconstrict
- \uparrow PR \rightarrow \uparrow BP
- \downarrow B flow to kidney
- \uparrow SBP • \uparrow DBP

N.B Baroreceptors found
in aortic arch and
Carotid artery. These
Receptor feel B-P if \uparrow BP
so send impulses to CNS \rightarrow
impulses by vagal nerve to
Heart to \downarrow Rate (Chronotropic)
not Affect Contractility (Inotropic)

But if muscarinic R of Heart
Blocked (Atropine) so vagal
impulses not reach to Heart
 \rightarrow Tachycardia

This called

Effect of Atropine pre III

B Therapeutic uses

III of shock as \uparrow BP and \uparrow Vascular R

But Dopamine more preferred why??
as it doesn't \downarrow kidney Blood flow -

@ actions

→ i) CVS

→ Vasoconstriction : it causes rise in peripheral resistance due to vasoconstriction of most vascular beds including the kidney by α_1 effect

→ Both systolic, diastolic blood pressure increase.

Baroreceptor reflex :

- * we have baroreceptor which are present in aortic arch, carotid artery

- * these receptors feel the blood pressure

- * if it \uparrow → these receptors send impulses to CNS which send impulses to the heart through vagal nerve to \downarrow its rate.

- * this action counteracts the local actions of norepinephrine on heart although it doesn't affect the positive inotropic effects on heart.

→ if we block the M receptors of heart → the vagal impulse won't reach the heart → then the effect of norepinephrine will appear as tachycardia, this is known as effect of atropine pretreatment

(b) Therapeutic effects

→ it's used to treat shock as it \uparrow BP by \uparrow vascular resistance.

But → dopamine is better as it doesn't reduce the blood flow to the kidneys as norepinephrine does

Epinephrine

③ Iso proterend (Isoprenaline)

- Synthetic Catecholamines

- more potent for β R as contain CH₃ GP. less selective for β_1, β_2 R

A Actn

① CVS

+ve Inotropic β_1
+ve Chronotropic
+ \uparrow Cardiac output
 \uparrow SBP - \downarrow DBP
 \downarrow mean arterial BP

② Respiratory S.

Broncho Dila \tilde{n} β_2
by inhalat \tilde{n}

③ hyperglycemia

④ lipolysis

B Therapeutic use

① Acute Pulmonary asthma

② Heart stimulant in emergency situat \tilde{n}

C Pharmacokinetics

- Parentally
- inhalat \tilde{n}
- sublingual
- deActivated by COMT
resistant to MAO

D Adverse effect

- ① CNS disturbance
- ② Pulmonary edema
- ③ cerebral Hemorrhage
- ④ Cardiac arrhythmia.

③ Isoproterenol

- ① actions
- ② Therapeutic uses.
- ③ Pharmacokinetics
- ④ adverse effects.

- * it's direct, synthetic catecholamines.
- * it stimulates β_1 , β_2 with low selectivity. (disadvantage)
- * its action on α receptors is insignificant.

① Actions

- i) Cardiovascular
- ii) respiratory.
- iii) others

i) Cardiovascular :

- it \uparrow rate, Force of contractility
∴ \uparrow Cardiac output. (β_1)
- it dilates the arterioles of skeletal muscles (β_2)
∴ it \downarrow peripheral resistance.
- ∴ it \uparrow systolic BP, \downarrow diastolic BP, \downarrow the mean arterial BP.

ii) Pulmonary :

- Bronchodilator, (β_2) effect → used in asthma (acute).
- It's taken by inhalator.

iii) other effects :

- other actions on β receptors are :
 \uparrow Blood sugar, \uparrow Lipolysis
- But they aren't significant clinically.

⑥ Therapeutic uses

- * it's now rarely used as bronchodilator in asthma.
- * it can be used as heart stimulant in emergency situations.

⑦ Pharmacokinetics

absorption :

- it's absorbed systemically by sublingual mucosa
- it's more " " " parenteral route, inhalation,

Metabolism :

- it's a Marginal Substrate for COMT
- , it's stable to MAO

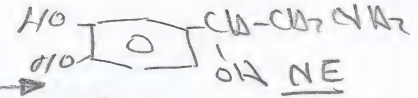
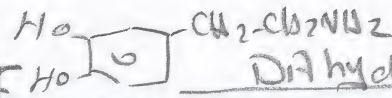
⑧ Adverse effects

→ Similar to that of epinephrine.

- ① CNS disturbances
- ② haemorrhage.
- ③ Cardiac arrhythmias
- ④ Pulmonary edema

④ Dopamine

- it is immediate precursor of N-E
- naturally occurred in basal ganglia and adrenal medulla secretion
- \downarrow Dose $\rightarrow \beta$ Receptor \rightarrow Vaso dilatation (Cardiac)
- \uparrow Dose $\rightarrow \alpha$ " \rightarrow " constriction
- not only α, β Receptor But also $D_1 - D_2 R$ in mesentery renal vascular beds - why??
 \rightarrow Presynaptic



A Act

- +ve Inotropic β_1
- +ve Chronotropic β_1
- \uparrow C. output
- $\alpha_1 \rightarrow$ Vaso Constriction
- $D_1, D_2 \rightarrow$ Dilatation
- \uparrow renal B flow
- N.B D_1, D_2 not affected. $\bar{\alpha}, \beta$ Blocker

B Therapeutic use

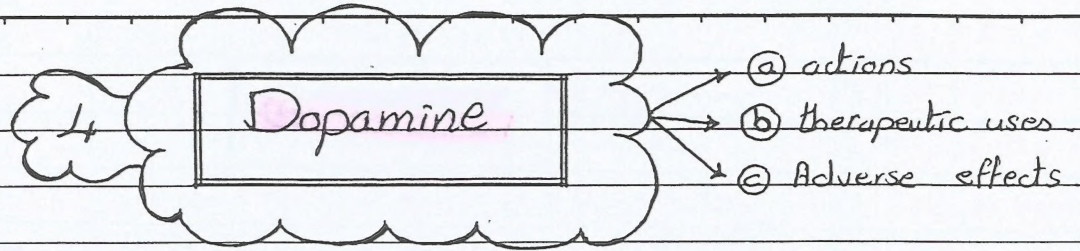
- ① III of shock where required \uparrow Heart Activity \bar{e} out Stop Renal function

N.B Dopamine more preferred Than epinephrine

C Adverse effect

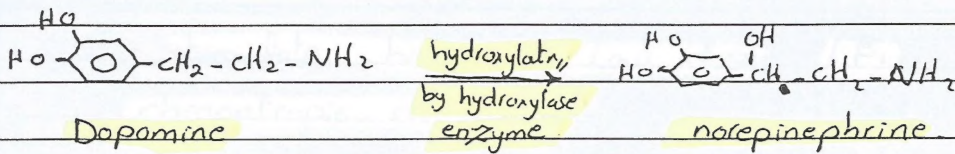
- D Pharmacokinetics \rightarrow Short ^{half-} life
- rapidly metabolized into Homovanillic acid

\downarrow
Nausea
Vomiting
Arrhythmia



* It's the immediate precursor of norepinephrine

(ی) ما قبل آدرین



* It occurs naturally in CNS in basal ganglia, in adrenal medulla secretion

در بافت بطنی و در غده آدرنال
Adrenaline

* it can act on both α , β adrenergic receptors
 \rightarrow at high doses \rightarrow affects α , \rightarrow vasoconstriction
 \rightarrow " Low " \rightarrow " β , cardiac receptors

* also it acts on dopaminergic receptors (D_1 , D_2) which are present only in peripheral mesenteric, renal vascular beds

ال D_1 , D_2 دو نوع آدرنرژیک receptors موجوده فقط في
 Kidney و في mesentery و يعمل vasodilatation في Blood vessels
 دي و لذلك في أثناء ال Adrenergic ال Blood Flow في Kidney
 من قبل او تحت مسخيم dopamine effect که او مستقیم ای transmitter
 تانی و من هیئتوا علی ال D_1 , D_2 که هیئتوا علی ال α و هیئتوا
 Blood vessels و Blood Flow دي و فیهل ال Blood Flow في Kidney
 و ممکنه تعمل Kidney shut down او shock induced by symp. activity

* also D_2 receptors mediates presynaptic inhibition

* بقیه عصبی نویسم مع ال receptors. بیهلوا α_2 , D_2 و presyn. inhib.
 آوی تناسم و دکتور آس. بیهلوا الحاجات دي آوی.

(a) actions

→ i) CVS

i) CVS :

- ⊗ → stimulate heart in low doses (β_1) → +ve inotropic, chronotropic effect.
- ⊗ → at high doses → vasoconstriction, (α_1)
- ⊗ → dilates renal, splanchnic arterioles → D_1, D_2 receptors
 - ∴ ↑ blood flow to kidneys, other viscera → these D_1, D_2 aren't affected by α, β blockers
- ∴ Dopamine is useful in shock treatment → where heart activity is required to ↑
- kidney function, is required not to stop.

(b) Therapeutic uses

→ i) shock treatment

i) Shock treatment :

- Dopamine is the drug of choice for shock given as continuous infusion
- it raises BP by heart stimulation, (β_1)
- it enhances perfusion to kidney → enhances glomerular filtration rate, causes Na^+ diuresis
- ∴ dopamine is preferred to epinephrine, norepinephrine as they diminish kidney blood supply, may cause kidney shutdown.

(C) Adverse effects

* → Dopamine overdose produces sympathetic then it's rapidly metabolized to homovanillic acid whose adverse effects are :

- ① Nausea
- ② hypertension
- ③ Arrhythmias

∴ short-lived action.

أحنا عارفين إن كره استهبال و المحاضرة كره ملهاني حل
لكن من السنة اللي فاتت أخذوا المنهج في ١٣ محاضرة وإحنا
هناخذ ١١ محاضرة فقط

لذلك المحاضرة دي تقدر تعتبرها محاضرتين من محاضرة ٣٦ صفحة
والأخرى ٢٠ صفحة من أسئلة تفهم على نفسك من كره لو اعتبرتها
محاضرة واحدة من صفحة هتتقدر وصلي هتقدر تناكرها

وبيقسم الجزء الأول بيتكلم عن موضوع ال Anti-cholinergic agents
والجزء الثاني بيتكلم عن ال Adrenergic receptors , adrenergic agonists

من يعني من هتخس حاجة لو قسمت المحاضرة إلى جزئين من وه أسئلة تفهم
نصيحة أخيرة يعني

من وأخيراً من أرجوكم أرجوكم من طلبنا المعارة : ادعوا لنا من بتفهم
معانا جداً جداً جداً

Dr. / K.A.

Dr. / P.S.

⑤ Dobutamine

- Synthetic Catecholamines
- Selective β_1 Receptor

A Actn

β_1 effect \rightarrow

\uparrow Cardiac output \bar{e}
little \uparrow in Heart rate

$$\bar{e} \text{ CoP} = \text{Stroke Volum} \times \text{HR}$$

\uparrow \downarrow \uparrow

$\bar{e} \uparrow$ Stroke Volum

This is imp. in Coronary artery problems

So it Doesn't \uparrow O_2 demands of myocardium

Adv over all
sympathomimetics

CC-HF

B Therapeutical use

\uparrow CoP - \uparrow HR \rightarrow
in Congestive Heart failure

Selective

β_1

\downarrow

dobutamine

β_2

\downarrow

Terbutaline

C adverse effect

- Epinephrine Ad.

- CNS disturbance
- Pulmonary edema
- arrhythmia

- Cerebral Hemorrhage

Used \bar{e} Caution \bar{e} Case
(arterial fibrillation)

due to \uparrow A-V conductn